Dr. Jonathan A. Cooper

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Fred Hutchinson Cancer Research Center
Basic Sciences
Member
University of Washington
School of Medicine
Biochemistry
Affiliate Professor

Mailing Address

Fred Hutchinson Cancer Research Center, A2-025
1100 Fairview Avenue N.
Seattle, Washington 98109
United States

Contact Information

Phone: (206) 667-4454
Fax: (206) 667-6522
jcooper@fhcrc.org

Qualifications

Ph.D., University of Warwick, 1976.
B.A., University of Cambridge, 1973.

Expertise and Research Interests

Cellular behaviors such as differentiation, proliferation, survival and migration are coordinated through cell-cell and cell-substrate interactions and by secreted factors. Many such signals are transmitted by tyrosine phosphorylation events, catalyzed by non-receptor and receptor tyrosine kinases. Although we know much about how tyrosine kinases are regulated and proteins they phosphorylate, many questions remain as to how they regulate cell behavior.

Recent efforts in the lab are directed towards identifying the functions and understanding the biochemistry of the Disabled (Dab) family of intracellular signaling proteins. These are found in flies, worms and vertebrates, and contain a highly conserved PTB domain. Unlike classical PTB domains, the PTB domains of Dab family proteins bind to non-phosphorylated sequences. Such sequences are found in the cytoplasmic tails of members of the lipoprotein receptor family and a few other transmembrane proteins. Indeed, reverse genetics experiments performed in the lab show that Dab proteins function in common pathways with various lipoprotein receptors. However, the specific biological pathways are quite divergent.

We have found that mammalian Dab1 is specifically expressed in neurons and is tyrosine phosphorylated during embryonic development. Mice with Dab1 mutations have brains that are grossly malformed because neurons are misplaced. We now know that an extracellular protein, Reelin, is present in parts of the brain where neurons make migration decisions, and Dab1 is a critical component of the signal transduction machinery for responding to Reelin. Reelin binds to specific receptors and induces tyrosine phosphorylation of Dab1 by Src and the closely related tyrosine kinase Fyn. This

phosphorylation event is needed for the neuron to migrate appropriately. The Reelin receptors are related to lipoprotein receptors, which were previously thought to be only involved in protein traffic but in this case clearly are acting to transduce signals. Recently we found that Reelin induces a complex between Dab1 and the adaptor proteins Crk and CrkL, and thereby leads to tyrosine phosphorylation of a Rap1 guanine nucleotide exchange factor and to Rap1 activation. We are working to establish whether this pathway is important in vivo, to identify other molecules in this signaling pathway, and to determine how Src and Fyn are activated by lipoprotein receptors.

Mammalian Dab2 (a putative tumor suppressor) may also have signaling functions. We found that Dab2 gene disruption causes early embryonic lethality with defects characteristic of embryos with altered growth factor signaling and reduced uptake of maternal nutrients for the embryo. The Dab2 gene is required in extra-embryonic lineages (but not in the embryo itself) for normal development. Conditional deletion of the Dab2 gene in the embryo proper allows the production of overtly normal mice. However, these mice have defects in transport mediated by a lipoprotein receptor known as megalin. Dab2 binds to megalin and to various proteins thought to be involved in endocytosis. Dab2 localizes to the endocytic apparatus. Thus Dab2 appears to be a cargo selective import protein. The relationship between this function and its function in embryonic development is being investigated. We are also studying Dab function in C. elegans. Here, a Dab-related adaptor protein functions in a common pathway with lipoprotein receptors to regulate development of the egg-laying apparatus. Our results show that Dab is needed for efficient secretion of a growth factor, apparently by directing the anterograde transport of secretory vesicles. Other components of this pathway and its underlying biochemistry are being investigated.

Keywords

COS Keywords:

Biochemistry, Biochemistry, Proteins, Neurons.

Previous Positions

1995-2000, Co-Director, University of Washington, Graduate Program in Molecular and Cellular Biology
1995-2000, Co-Director, Fred Hutchinson Cancer Research Center, Graduate Program in Molecular and Cellular Biology

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